

# Abnormalities of interhemispheric functional connectivity in individuals with acute eye pain: a resting-state fMRI study

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## Abstract

• **AIM:** To study the changes of the resting state functional connectivity (rsFC) between acute eye pain (EP) subjects and healthy controls (HCs) in the two hemispheres by using voxel-mirrored homotopic connectivity (VMHC) method.

• **METHODS:** Totally 20 patients with EP and 20 HCs were enrolled, sex, age, and education were matched, and all subjects were examined by functional magnetic resonance imaging (fMRI) scans at resting-state. The changes of rsFC between the hemispheres were evaluated by the VMHC method according to Gaussian random field (GRF) theory. In order to identify the VMHC, as biomarkers for distinguishing EP and from HC, the receiver operating characteristic curves (ROC) had been analyzed. The relationships were evaluated with Pearson correlation analysis between the mean VMHC signal values and clinical features in these patients.

• **RESULTS:** By comparing with health subjects, the significant decreased VMHC values was observed in lingual/calcarine (Brodmann area, BA 30), precentral/postcentral gyrus (PreCG/PosCG; BA 4) and medial frontal

gyrus (MFG; BA 8) (false discovery rate corrected <0.01) in the acute EP individuals. The accuracy of area under curve was excellent indicated by the ROC curve analysis of each brain regions.

• **CONCLUSION:** Our study demonstrates preliminary evidence of disrupted interhemispheric rsFC in acute EP in sensorimotor and limbic system and somatosensory cortex, which might give some useful information for understanding the neurological mechanisms in acute EP individuals.

• **KEYWORDS:** acute eye pain; voxel-mirrored homotopic connectivity; functional magnetic resonance imaging; resting state

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## INTRODUCTION

Acute eye pain (EP) is a very common ocular symptom in many ophthalmic diseases such as keratitis, ocular trauma and glaucoma *et al.* The cornea pain is one of the most common kinds of EP, and is always strong sharp, and causing visual disability. As a densely innervated structure, the cornea is one of the most sensitively tissues, which is supplied by the trigeminal nerve with the ophthalmic branch. Thus, infectious keratitis and corneal ulcer can cause serious EP. In China, the prevalence reported by other researcher was 0.148% in infectious keratitis<sup>[1]</sup> and the cornea pain always be the most frequently complain in keratitis patients. Cornea pain not only leads to the ocular discomfortable, but also might lead to the psychological disorders such as depressive and anxiety symptoms<sup>[2]</sup>.

For corneal pain, the direct cause is that the damage of the cornea nerve triggers peripheral and central trigeminal sensory networks. Whether acute EP was processed at the level of the cortex remains unknown. In order to evaluate the alteration of intrinsic brain activity, functional magnetic resonance imaging (fMRI) had increasingly been applied in acute and

chronic pain. Mathur *et al*<sup>[3]</sup> reported that the acute migraine pain individuals involved in cognitive-related neural activity changes. Increased function connectivity between insula and the anterior cingulate and the hippocampus were observed in the acute pressure pain<sup>[4]</sup>. Moreover, the anterior cingulate, primary sensory and motor cortex activity were involved in acute and persistent pain<sup>[5-6]</sup>. The chronic pain not only leads to brain function change but also lead to abnormalities of brain structure. Duke Han *et al*<sup>[7]</sup> demonstrated that increased functional connectivity occurred in the chronic pain between the left insula and posterior cingulate. The reduced grey matter volume was supposed to be associated with trigeminal neuralgia in the primary somatosensory and orbitofrontal cortices compared with health controls<sup>[8]</sup>. Yet it is little known on the resting state functional connectivity (rsFC) between homotopic regions in the whole brain in acute EP.

Hemispheric specialization is a notable feature of the human brain and is involved in memory<sup>[9]</sup>, cognition<sup>[10]</sup> and emotion<sup>[11]</sup>. Thus, hemispheric specialization provides a crucial evidence for neurophysiological mechanism. It has been reported previously that the fMRI imaging in EP patients has successfully been applied to assess the neurophysiological changes. It is a useful method by using fMRI analysis at resting-state to assess activity of regional brain during rest with amplitude of low-frequency fluctuation (ALFF)<sup>[12-13]</sup>, which is a reliable and reproducible method<sup>[14-15]</sup>. Our previous study has found abnormal ALFF in the precentral gyrus, and left precuneus, left caudate and parahippocampal gyri in patients with acute EP<sup>[16]</sup>. Meanwhile, it's well known that visual sensation is strongly associated with interhemispheric synchrony<sup>[17]</sup>. The voxel-mirrored homotopic connectivity (VMHC) method, an fMRI technology at resting state, was applied to evaluate the rsFC both in the functional hemisphere and its counterpart in the opposite part with the time series for a given voxel<sup>[18]</sup>. A previous VMHC study reported that decreased interhemispheric connectivity in the precuneus, the dorsolateral prefrontal and posterior cingulate cortex were studied in postherpetic neuralgia individuals<sup>[19]</sup>. However, so far, whether alterations of interhemispheric functional synchronization occur in EP subjects is still unknown.

Here, our aim of this study was to explore changes of interhemispheric rsFC in acute EP individuals by the VMHC analysis method. We speculated that acute EP might be correlated with the disrupted rsFC in the interhemispheric part. Furthermore, whether the mean VMHC values can be used as a useful clinical biomarker for acute EP.

## SUBJECTS AND METHODS

**Ethical Approval** In this research, the protocol in methods complied with the Declaration of Helsinki and conformed to the principles of Medical Ethics of the Ophthalmology

Department, the First Affiliated Hospital of Nanchang University and the Ophthalmology Department of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. Informed consent forms were provided to all volunteers.

**Participants** Totally 20 patients were recruited, and all of them were with acute EP (5 females and 15 males), from the Ophthalmology Department in the First Affiliated Hospital of Nanchang University and the Ophthalmology Department from the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. The inclusion criteria of acute EP subjects in the study were: 1) acute EP patients due to corneal ulcers or keratitis; 2) bilateral eye involvement, with no ophthalmic diseases, such as myopia, cataracts, strabismus, optic degeneration, uveitis, retinal diseases, *etc.*

In our study, the exclusion criteria for EP were listed as follows: 1) chronic symptoms with EP, more than three months; 2) ocular trauma related EP; 3) EP patients with a history of painkiller treatment before MRI scan; 4) serious complications related EP such as endophthalmitis, ocular perforating, orbital cellulitis, *et al*; 5) EP patients were complained with headache or pains from other body parts; 6) cardiovascular system diseases related EP, heart disease, hypertension, and so on; 7) psychiatric related problems and infarction diseases in cerebra (cerebral vascular malformations, infarction and hemorrhage cerebral disease).

There were 20 healthy controls (HCs; 5 females and 15 males) enrolled in the study and they were closely matched in demographics information such as sex, age, and education level to the EP subjects. All health subjects followed the listed criteria: 1) with no eye problem and the best corrected visual acuity above 1; 2) no psychiatric related disorders (such as bipolar disorder or depression, and so on); 3) had no cardiac pacemaker or metal devices implanted in body and so on, all of which ensured the HCs be able to be examined with MRI scan.

**Magnetic Resonance Imaging Data Acquisition** All participants were examined by MRI on a 3.0T system which had eight-channel head coil (Siemens, Munich, Germany). Under spoiled gradient-recalled echo sequence, the T1-weighted whole-brain scans were performed with the parameters: (thickness=1.0 mm, repetition time at 1900ms, acquisition matrix with 256×256, echo time at 2.26ms, view field: 250×250 mm<sup>2</sup>, gap=0.5 mm, flip angle=9°). During 8-min resting-state scan with parameters as follows (echo time at 30ms, repetition time about 2000ms, gap=1.2 mm, thickness=4.0 mm, acquisition matrix with 64×64, flip angle=90°, 29 axial, view field=220×220 mm<sup>2</sup>) covered whole brain were corrected. During the fMRI scan, each participant was keeping awake during the whole examination.

**Data Preprocessing in Functional Magnetic Resonance Imaging** As shown in previous studies<sup>[20-21]</sup>, the functional data was entered into the Data Processing Assistant, which was designed as Resting-State fMRI (rs-fMRI) Advanced Edition (DPARSFA; <http://rfmri.org/DPARSFA>)<sup>[20]</sup> and Statistical Parametric Mapping (SPM8; refer to <http://www.fil.ion.ucl.ac.uk/spm>) on the basis of MATLAB2013a (Mathworks, Natick, MA, USA).

**Statistical Analysis in Voxel-mirrored Homotopic Connectivity** In order to correct the normality, the VMHC maps in individuals were converted to z values by applying a Fisher z-transformation in the REST software (<http://resting-fmri.sourceforge.net>). As shown in a previous study<sup>[18]</sup>, a random effect of two sampled *t*-test was applied to analyze z-maps in individual to identify the changes in VMHC between two groups, in a voxel-wise manner with the global VMHC as covariate. The voxel level ( $P < 0.05$ ) was set as the statistical threshold for the multiple comparisons with Gaussian random field (GRF) theory ( $z > 2.3$ , cluster  $> 40$  voxels,  $P < 0.01$ , corrected FDR).

**Statistical Analysis** In this study, the cumulative clinical measurements were statistically analyzed with independent sample *t* test with the SPSS software (SPSS version 16.0, Inc., Chicago, IL, USA). With the SPM8 toolki, the analysis of general linear model was performed for the statistical analysis, and the paired *t*-tests was applied to evaluate the changes in the z-maps of VMHC between the health controls and the EP groups. The receiver operating characteristic (ROC) curves was applied to evaluate the changes in the mean values of the VMHC from different brain regions between EP and healthy individuals. The relationship of behavioral performances and the mean values of VMHC in different brain regions was illustrated by Pearson correlation between the EP group and healthy subjects ( $P < 0.05$  with significant differences).

**RESULTS**

**Demographics and Visual Measurements** In the study, we don't found any significant differences for age with  $P = 0.796$  and for weight with  $P = 0.845$ , between the HCs and acute EP individuals ( $P > 0.05$ ). The duration for EP was  $13.17 \pm 6.21$  d showed in the mean  $\pm$  standard deviation (Table 1).

**Voxel-mirrored Homotopic Connectivity Differences** By compared to HCs, the VMHC decreased in acute EP individuals in lingual/calcarine, and medial frontal gyrus (MFG) and precentral/postcentral gyrus (PreCG/PosCG) (Figure 1, Table 2). In these two groups, we found the mean values of VMHC altered, and the values were displaced in a histogram (Figure 1C). In the EP individuals, our results showed no association between their clinical symptoms and the mean values of VMHC in different brain regions with  $P > 0.05$  showed no significant difference.

**Table 1 Demographics and clinical measurements for EP and HC group**

Condition	EP	HC	<i>t</i>	<i>P</i> <sup>a</sup>
Female/male	5/15	5/15	N/A	>0.99
Age (y)	52 $\pm$ 5	51 $\pm$ 5	0.260	0.796
Weight (kg)	63.56 $\pm$ 7.12	63.18 $\pm$ 6.68	0.197	0.845
Handedness	20R	20R	N/A	>0.99
Duration of EP (d)	13.17 $\pm$ 6.21	N/A	N/A	N/A

EP: Eye pain; HC: Healthy control; N/A: Not applicable. <sup>a</sup>Independent *t*-tests comparing two groups.

**Table 2 Brain areas demonstrated significantly different VMHC values between EP and HC group**

Brain regions/ conditions	BA	MNI coordinates			Cluster size	<i>t</i>
		X	Y	Z		
EP<HCs						
Lingual/Calcarine	30	$\pm 12$	-63	-9	65	-4.529
PreCG/PosCG	4	$\pm 54$	-15	48	128	-3.692
MFG	8	$\pm 3$	36	39	48	-5.123

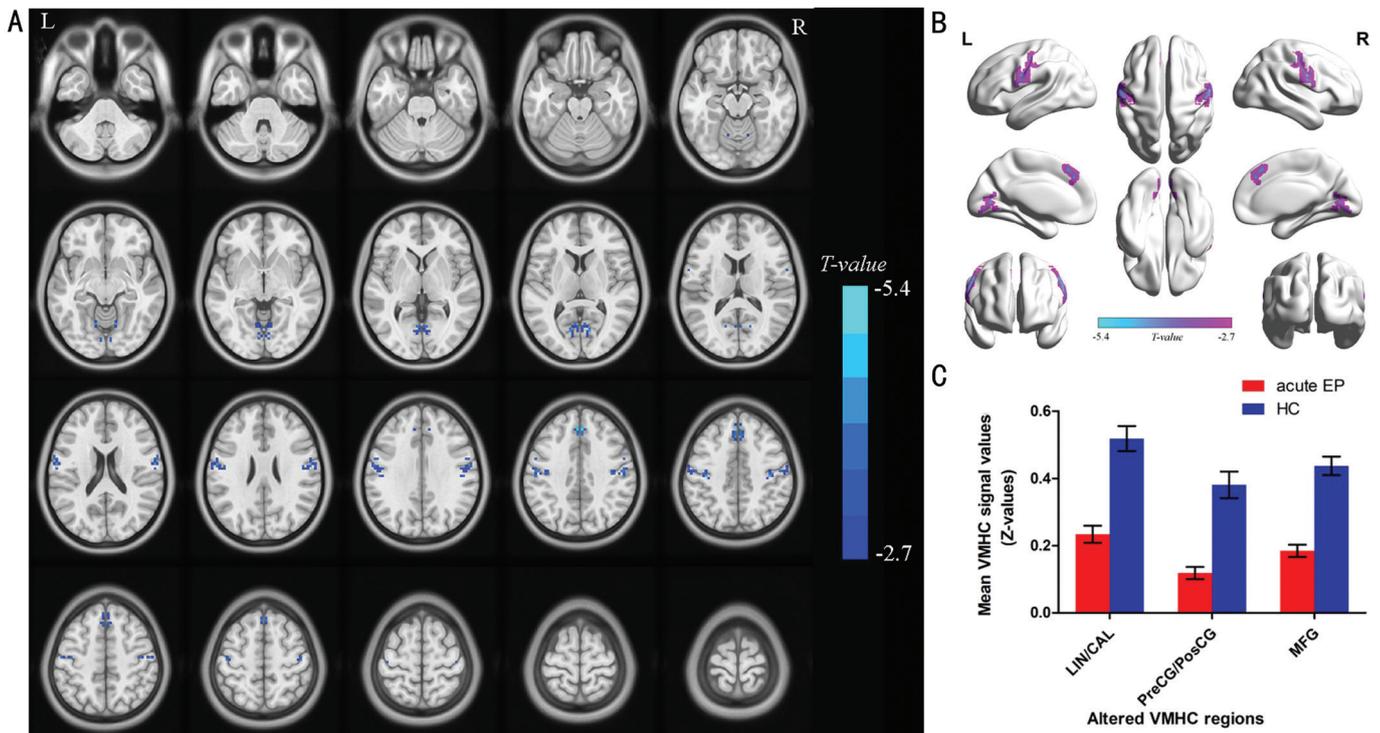
VMHC: Voxel-mirrored homotopic connectivity; EP: Eye pain; HC: Healthy control; BA: Brodmann area; MNI: Montreal Neurological Institute; MFG: Medial frontal gyrus; PreCG/PosCG: Precentral/postcentral gyrus.

**Receiver Operating Characteristic Curve** Our study speculated that by comparing the differences between the EP and HCs individuals, the VMHC might be a very useful clinical markers. Furthermore, the mean VMHC values were compared and analyzed by the ROC curves method in different brain areas. The under ROC curve area (AUCs) stands for diagnostic rate. The AUCs for VMHC values were 0.933 with  $P < 0.001$ , and the 95%CI about 0.731-0.984, for lingual/calcarine; PreCG/PosCG was 0.938 ( $P < 0.001$ , 95%CI: 0.704-0.961); for MFG (0.990;  $P < 0.001$ ; 95%CI: 0.786-0.999), showed in Figure 2, EPs<HCs.

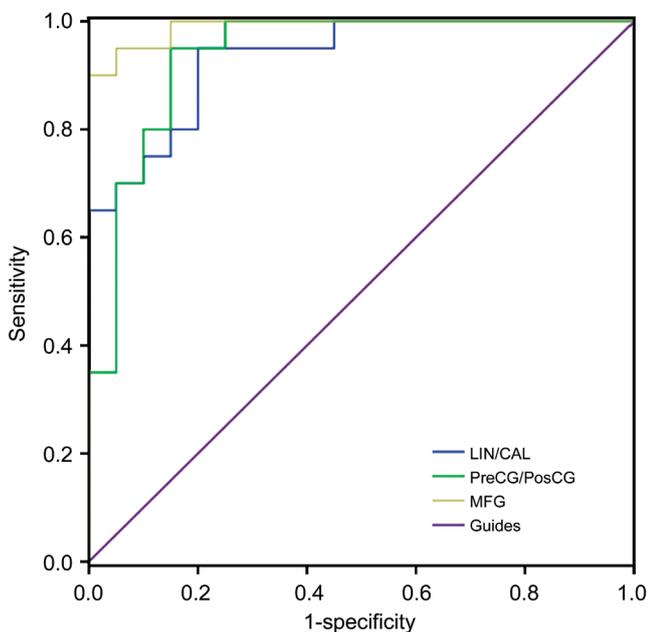
**DISCUSSION**

As we known, the VMHC is a novel and reliable rs-fMRI method to illustrate the alterations of functional interhemispheric connectivity. Our study is the first to explore the functional interhemispheric connectivity involved in acute EP individuals. In this research, comparing with HCs, the significant decreased VMHC values were observed in the bilateral parts of lingual/calcarine, bilateral PreCG/PosCG and bilateral MFG in the acute EP individuals (Table 2). Compared with HCs, the following regions demonstrated very significantly increased DC values to various extents: 1-lingual/calcarine (L; BA30,  $t = -4.529$ ), 2-lingual/calcarine (R; BA30,  $t = -4.529$ ), 3-(PreCG/PosCG) (L;  $t = -3.692$  for BA), 4-(PreCG/PosCG) (R; BA4,  $t = -3.692$ ), 5-MFG (L; BA8 with  $t = -5.123$ ) and 6-MFG (R; BA8,  $t = -5.123$ ) in acute EP individuals (Figure 3).

Lingual gyrus and calcarine sulcus are both parts of the occipital lobe. The primary visual cortex (V1) concentrated

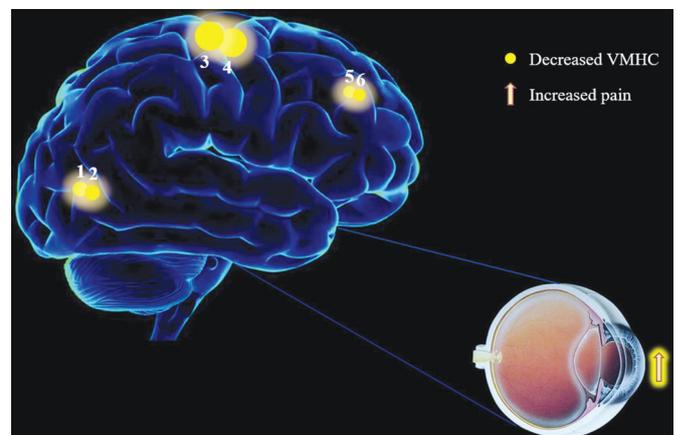


**Figure 1 Interhemispheric connectivity in the EPs versus HCs** A: The lower VMHC values was indicated by blue areas showed  $P < 0.01$  for multiple comparisons analyze within GRF theory,  $P < 0.01$ ,  $z > 2.3$ , cluster above 40 voxels with corrected FDR; B: The mean VMHC values were altered between the EPs and HC individuals; C: The differences observed in the interhemispheric connectivity were significant in the lingual/calcarine, PreCG/PosCG, MFG.



**Figure 2 The analysis of ROC curve in the mean values of VMHC for different brain regions.**

in the calcarine sulcus as reported<sup>[22]</sup>, and the lingual gyrus located between the posterior part of the collateral sulcus and the calcarine sulcus, which plays a very important role in vision and dreaming<sup>[23]</sup>. Various neuroimaging studies demonstrated that the occipital lobe was related to many chronic pain processes including headache and low back pain<sup>[24-25]</sup>. Moreover, a VBM study reported that chronic low



**Figure 3 The VMHC results of brain activity in the acute EP individuals.**

back pain individuals were supposed to be closely associated with the decreased volume in occipital lobe by gray matter<sup>[26]</sup>. Meanwhile, Cutrer *et al*<sup>[27]</sup> revealed that the migraine patients displaced cerebral blood flow reduction in the occipital cortex. In this study, acute EP individuals displaced that VMHC values decreased in lingual/calcarine, which indicated impaired function of interhemispheric functional connectivity in lingual/calcarine. Therefore, it supposed to be that acute EP in individuals might lead to interhemispheric dysfunction in pain processes brain region.

Primary somatosensory cortex (S1) was found to be located in postcentral gyrus, which is correlated with sensation<sup>[28]</sup>.

Meanwhile, the S1 play a very critical role in the processes sensation of pain<sup>[29]</sup>. A recent research reported that functional and structural plasticity of S1 occurred in chronic pain individuals<sup>[30]</sup>. An fMRI study revealed that corneal pain subjects showed activations in S1 and primary motor cortex<sup>[31]</sup>. Moreover, a phantom limb pain patient showed increased sensitivity of S1 to pain-related<sup>[32]</sup>. In our study, our results exhibited that significant decreased VMHC values was observed in postcentral gyrus, which indicated that EP individuals might associate with hemispheric specialization dysfunction in S1.

Precentral gyrus, known as primary motor cortex (M1), which played a very essential role in motor control. Many previous studies demonstrated that the dysfunction of M1 occurred in complex regional pain syndrome<sup>[33]</sup>. A neuroimaging study revealed that acute muscle orofacial and cutaneous pain were highly associated with signal change within the contralateral M1 in form of intensity decreases<sup>[34]</sup>. Meanwhile, acute muscle pain led to the altered activity in S1/M1<sup>[6]</sup>. In our research, the results showed that acute EP individuals demonstrated significant decreased VMHC values in bilateral precentral gyrus. That is to say, the EP individuals might associate with impaired hemispheric specialization in M1.

MFG is involved in higher cognitive function. The MFG played a critical role in executive and cognition function<sup>[35]</sup>. Our results exhibited that significant decreased VMHC values were observed in the bilateral MFG in individuals with acute eye pan. We speculated that acute pain in eye might cause the dysfunction in cognition.

ROC curve provides a standardized and statistical method to distinguish disorder condition from healthy individuals. When an AUC value is 0.7-0.9, the accuracy is perceived as perfect. A value between 0.5 and 0.7 is considered moderate, and less than 0.5 means the discrimination result is low. The analysis of ROC curve in our research showed that the AUCs of each brain regions were over 0.9, which might represent these specific VMHC differences have a proper diagnostic accuracy in identifying EP. In brief, these results showed that the method of the VMHC might be a sensitive measurement of rs-fMRI, indicating that the lingual gyrus/calcarine, PreCG/PosCG and MFG might be appropriate clinical markers for EP patients in future. In sum, our research suggested that individuals with acute EP demonstrated impaired hemispheric specialization in the M1/S1 regions, the limbic system and emotion regions, which could possibly provide primarily evidences to explain the neurological mechanisms involved in sensorimotor and emotion dysfunction in EP individuals.

Some limitations should be mentioned in our research. First of all, the relatively small sample size should be taken into account. Second, our study did not find the relationship

between their clinical features and the mean values of VMHC in many brain areas. Third, in this study, the VMHC methods were applied to investigate hemispheric specialization changes in acute EP individuals. Future study, multi-modal methods of neuro imaging should be used to illustrate the alterations of brain activities.

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